Long-term Glycaemic Control Directly Correlates with Glomerular Filtration Rate in Early Type 1 Diabetes Mellitus Before the Onset of Microalbuminuria

C.P.R. Soper*[1], J.L. Barron[2], S.L. Hyer[3]

[1]*Southwest Thames Renal Unit, St Helier Hospital, Carshalton, Surrey, UK*
[2]*Department of Chemical Pathology St Helier Hospital, Carshalton, Surrey, UK*
[3]*Diabetes Centre, St Helier Hospital, Carshalton, Surrey, UK*

Hyperfiltration occurs early in diabetes mellitus and has been implicated in the development of microalbuminuria. Our aim was to re-examine the controversial relationship between glycaemic control and glomerular filtration (GFR) in normoalbuminuric, normotensive, non-obese patients with short duration Type 1 diabetes mellitus (DM). We studied 75 Type 1 DM patients, 35 male, aged 18–42 years, with a duration of diabetes of 4–8 years. GFR was determined by inulin clearance; hyperfiltration was defined as above 145 ml min^{-1} 1.73 m^{-2} (equivalent to 2 SD above mean for a control population). Analysis was by paired Student's *t*-testing and linear regression. GFR correlated significantly with HbA_{1c} ($r = 0.47$, $p < 0.0001$) and fructosamine ($r = 0.24$, $p = 0.035$). Mean HbA_{1c} and fructosamine in the 13 patients with hyperfiltration was significantly higher than in the rest of the group (HbA_{1c}: 9.2 % (95 % C.I. 7.9–10.4 %) vs 7.6 % (7.2–7.9), $p = 0.002$; fructosamine: 479 μmol l^{-1} (450–507) vs 410 μmol l^{-1} (388–432), $p = 0.009$. This significant difference persisted even when the two highest values of HbA_{1c} or fructosamine were removed from analysis. Effective renal plasma flow, assessed by PAH clearance, also correlated in all patients with HbA_{1c} ($r = 0.31$, $p = 0.039$). We conclude that poor glycaemic control directly correlates with hyperfiltration and renal hyperperfusion in early Type 1 DM.

***Diabet. Med.* 15: 1010–1014 (1998)**

KEY WORDS **hyperfiltration; Type 1 diabetes mellitus; glomerular filtration rate; glycaemic control; insulin-like growth factor; cystatin C**

Received 6 August 1997; revised 4 June 1998; accepted 26 June 1998

Introduction

Previous studies have established a direct correlation between diabetic control and the development of microalbuminuria. In the primary prevention arm of the DCCT, patients on conventional diabetic treatment were 51 % more likely to develop persistent microalbuminuria (>28 μg min^{-1}) compared to those in whom treatment had been optimized.[1] The degree of association of early hyperfiltration with diabetic nephropathy remains controversial.[2,3] The association between glycaemic control and glomerular filtration rate (GFR) has also proven controversial[4,5] although many studies have examined patients over a broad span of duration of disease, including some before and after the development of microalbuminuria. By selecting patients with a narrow band of duration of diabetes prior to the onset of microalbuminuria we sought further to investigate the link between glycaemic control and GFR.

Patients and Methods

The outpatient records, computer database, and written notes for patients of five participating hospitals were searched. We selected patients who were 35 years old or less at diagnosis, insulin requiring within 6 months of presentation and between 4 and 8 years disease duration. Diagnosis was taken as the time of first requiring insulin therapy. Patients were excluded if they were: receiving medication that would lower blood pressure; had hypertension (>140/90 mmHg); showed marked obesity (BMI > 35); had documented persistent microalbuminuria, proteinuria or a history of renal disease.

GFR was determined by inulin clearance, using an infusion to steady state method of determination, appropriate for patients with hyperfiltration.[6] Infusion pump delivery was calibrated prior to clinical testing. For 12 h before testing, protein intake was kept below 10 g, no

Abbreviations: ERPF effective renal plasma flow, GFR glomerular filtration rate, IGF-BP insulin-like growth factor binding protein, PAH para-aminohippurate

Sponsors: St Helier NHS Trust Research and Development Fund

* Correspondence to: Dr Charles Soper, Southwest Thames Renal Unit, St Helier Hospital, Wrythe Lane, Carshalton, Surrey SM5 1AA, UK

 CCC 0742–3071/98/121010–05$17.50

caffeine or alcohol intake or smoking was allowed. The automated enzymatic assay is not prone to interference by glucose.[7] Hyperfiltration was defined as being above 145.0 ml min^{-1} 1.73 m^{-2}, being 2 standard deviations (SD) above the mean for a control population.[8]

Para-aminohippurate (PAH) clearance was determined simultaneously to evaluate effective renal plasma flow (ERPF).[9] Microalbuminuria was screened by the use of timed, overnight collections of urine. If a sample yielded an albumin excretion rate greater than 28 μg min^{-1}, a further collection was obtained. If this specimen also exceeded this threshold the patient was excluded. Urinary albumin content was analysed by immunoturbidimetry.[10] HbA_{1c}, fructosamine, glucose, insulin-like growth factor (IGF)-1, -2, and IGF Binding Protein (IGFBP)-1 and -3 were also measured at the end of the infusion.

IGF-1, IGF-2, IGFBP-1 and IGFBP-3 were determined by radioimmunoassay (RIA),[11,12] a commercial immunoenzymometric assay (Octeia Tyne and Wear, UK), or two site immunoradiometric assay (DSL, Texas, USA). Fructosamine was determined by colorimetry,[13] HbA_{1c} by cation exchange HPLC,[14] and Cystatin C by particle-enhanced immunoturbidiometry.[15]

Results were analysed by paired sample Student's *t*-testing and linear regression using the Systat 5.02 statistics package (Systat Inc., Illinois, USA). The trial protocol was approved by the local research and ethical committees in all 5 districts.

Results

Table 1 shows the characteristics of the 75 subjects. Only one screened patient was excluded because of microalbuminuria. The normal probability plot shows that the GFR distribution was near to normal (Figure 1). There was no evidence of a bimodal distribution and its skewness was 1.29.

Table 2 shows the glycaemic control of the study patients. There was correlation between glycaemic control whether judged by HbA_{1c} or fructosamine and GFR ($r = 0.47$ and 0.24, $p < 0.0001$, and 0.035, respectively). The scatter plots are shown in Figures 2 and 3.

Thirteen patients had glomerular hyperfiltration (Table 3). As a group, their control was significantly worse than

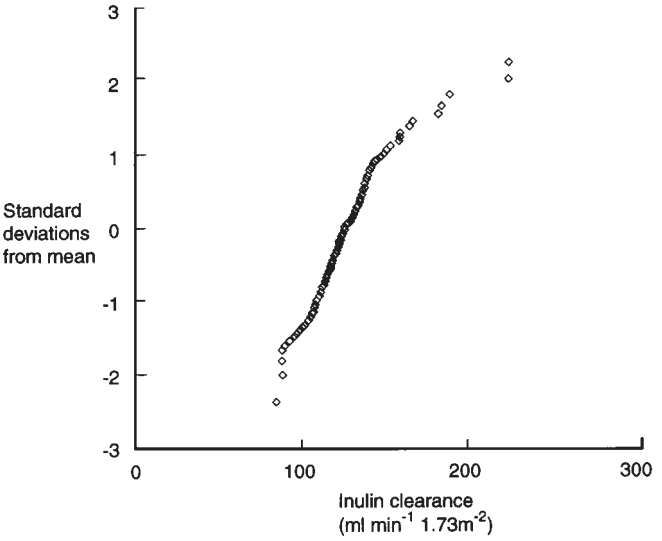

Figure 1. Normal probability plot for GFR

in patients with normal GFR ($p = 0.002$ for HbA_{1c} and $p = 0.009$ for fructosamine). If an arbitrary alternative cut off for hyperfiltration was taken either at 140 or 150 ml min^{-1} 1.73 m^{-2}, the comparison retained significance for both HbA_{1c} and fructosamine ($p = 0.001$ and <0.0001 for HbA_{1c}, $p = 0.0047$ and 0.008 for fructosamine). If the two highest values for HbA_{1c} or fructosamine were removed from the analysis the relationship retained significance ($p = 0.003$ or 0.002, respectively). However no relationship by any definition of hyperfiltration was evident between GFR and serum glucose concentration at the conclusion of the inulin clearance infusion. There was no evidence for a threshold value for such a correlation, in patients whose serum glucose was below 13.5 mmol l^{-1} or other proximate values.

ERPF correlated with HbA_{1c} ($r = 0.31$, $p = 0.039$) but not fructosamine ($r = 0.03$, $p = 0.8$). In 5 patients, intolerance to PAH occurred, despite using doses lower than those advised in the data sheet. Common side-effects were headaches, diplopia and one severe but delayed allergic reaction requiring admission. Its use was discontinued after 46 patients had been studied. Reciprocal Cystatin C showed no correlation with GFR

Table 1. Study patient characteristics, and the comparison of hyperfilterers with normofilterers

	All Patients	Normofiltering (<145.0 ml min^{-1} 1.73 m^{-2})	Hyperfiltering (≥145.0 ml min^{-1} 1.73 m^{-2})	Comparison between hyperfilterers and normofilterers
n	75	62	13	–
Age (years)	31 (19–42)	30 (19–39)	32 (21–42)	N.S.
Sex	35M 40F	29M 33F	6M 7F	N.S.
BMI (kg m^{-2})	23.8 (17.0–32.1)	24.3 (17.0–32.1)	23.0 (19.4–31.8)	N.S.
Daily mean insulin dosage (units kg^{-1})	0.65 (0.30–1.28)	0.65 (0.30–1.28)	0.68 (0.32–1.01)	N.S.

Results as median (range).

Table 2. Glycaemic control of all patients, normofilterers and hyperfilterers, and the comparison of hyperfilterers with normofilterers

	All patients	Normofiltering (<145.0 ml min^{-1} 1.73 m^{-2})	Hyperfiltering (≥145.0 ml min^{-1} 1.73 m^{-2})	Comparison between hyperfilterers and normofilterers
HbA_{1c}	7.9 % (7.5–8.3)	7.6 % (7.2–8.0)	9.2 (7.9–10.4)	$p = 0.002$
Fructosamine (μmol l^{-1})	422 (402–442)	410.4 (388–432)	479 (450–507)	$p = 0.009$
Serum glucose at 120 min (mmol l^{-1})	7.7 (6.6–8.8)	7.5 (4.9–8.6)	8.4 (6.0–10.8)	N.S.
Mean albumin excretion rate (μg min^{-1})	8.8 (7.6–10.2)	8.5 (7.1–9.9)	10.4 (6.3–12.8)	N.S.

Results as mean (95 % confidence interval).

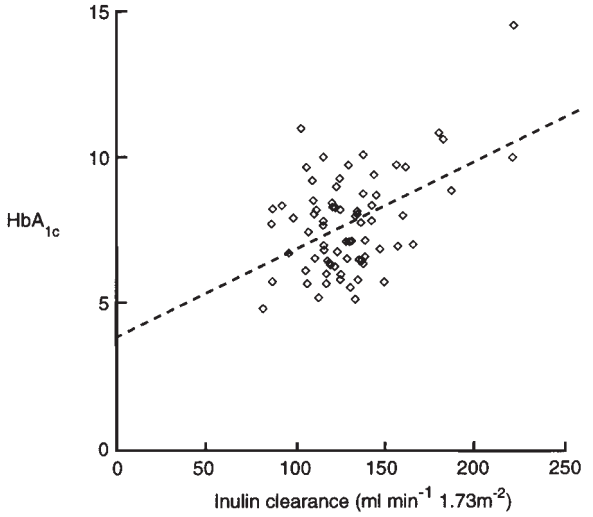

Figure 2. Scattergram plot of GFR vs HbA_{1c}

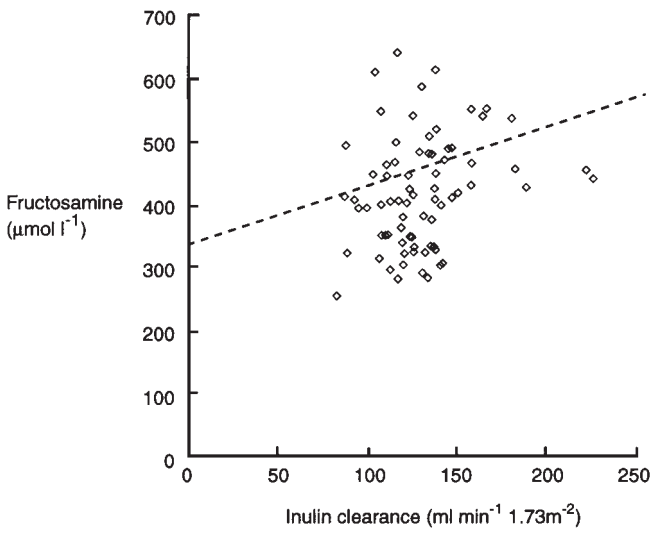

Figure 3. Scattergram plot of GFR vs fructosamine

and did not discriminate hyperfilterers from normofiltering patients.

We found a modest inverse correlation between IGF-1 and either HbA_{1c} or fructosamine ($r = -0.27$ and -0.34, $p = 0.02$ and 0.003, respectively). IGF-2, IGFBP-1, and IGFBP-3 showed no association with glycaemic control. No relation either with GFR or with ERPF was evident for these substances. Table 3 shows the renal haemodynamic and growth factor results for the hyperfilterers and the whole group are disclosed in Table 3.

One patient was found to have marked hyperfructosaemia, with values ranging from 0.67 to 0.75 mmol l^{-1} (the 95 % confidence interval for all other patients was 0.16–0.19 mmol l^{-1}). She had a BMI of 31.8, no symptoms of fructose intolerance or evidence of fructosuria. After excluding her results from the analysis, the correlation of HbA_{1c} and fructosamine with GFR remained significant ($r = 0.34$ and 0.25, $p = 0.004$ and 0.029, respectively) but not that between ERPF and GFR ($r = 0.14$, $p = 0.36$).

Discussion

Glomerular hyperfiltration in diabetes mellitus was first described in 1934.[16] Its relationship with glycaemic control has been controversial. One series reported a direct correlation with serum glucose at the time of GFR determination, provided it was below a threshold of 13.5 mmol l^{-1}, but no relation with HbA_{1c}.[4] This has not subsequently been confirmed.[17] In euglycaemic and hyperglycaemic clamp states, no significant short-term GFR changes were observed in either normofiltering or hyperfiltering Type 1 DM patients.[18] However parenteral glucose infusion has been found to augment GFR modestly.[19] In the present study, we have not found any relationship between renal function and serum glucose, either absolutely or modulated by a threshold effect. We did however find a robust correlation between GFR and indices of longer term glycaemic control, in a cohort of tightly selected patients, confirming a similar report from a slightly smaller sample.[5] Unlike our own data, this latter study did not find a relation between GFR and fructosamine. Its inclusion of patients with a long duration of disease with normoalbuminuria may have resulted in under-representation of an important subset of patients, namely those likely to develop early nephropathy.

While not within its primary remit, the DCCT detected a non-significant trend to a reduction in iothalamate clearances in the treatment group after implementation of strict control in both study cohorts ($p = 0.08$ for primary prevention, and $p = 0.094$ for secondary prevention).[1] Enhanced control by continuous subcutaneous insulin infusion results in a reduction in GFR over at least a year.[20,21] This is consistent with our findings that sustained glycaemic control, rather than short-term

Table 3. Renal haemodynamic and growth factor results of all patients, normofilterers and hyperfilterers, and the comparison of hyperfilterers with normofilterers

	All patients	Normofiltering (<145.0 ml min^{-1} 1.73 m^{-2})	Hyperfiltering (≥145.0 ml min^{-1} 1.73 m^{-2})	Comparison between hyperfilterers and normofilterers
GFR	129.0	119.9	172.5	–
(ml min^{-1} m^{-2})	(122.9–135.1)	(116.1–123.8)	(158.2–186.8)	
ERPF[a]	574	555	641	N.S.
(ml min^{-1} m^{-2})	(523–624)	(503–608)	(512–770)	
Filtration fraction[a]	0.24	0.23	0.27	N.S.
	(0.21–0.26)	(0.20–0.26)	(0.22–0.32)	
IGF-1	0.57	0.59	0.48	N.S.
(IU ml^{-1})	(0.51–0.63)	(0.52–0.66)	(0.36–0.59)	
IGF-2	0.78	0.77	0.87	N.S.
(IU ml^{-1})	(0.74–0.83)	(0.72–0.82)	(0.77–0.96)	
IGF BP1	20.9	18.2	31.0	N.S.
(mg l^{-1})	(13.7–28.1)	(13.1–23.3)	(2.6–59.3)	
IGF BP3	2.94	2.87	3.28	N.S.
(mg l^{-1})	(2.65–3.23)	(2.56–3.18)	(2.55–4.01)	

[a] $n = 46$ (see text).
Results as mean (95 % confidence interval).

fluctuation, is the main influence upon GFR. The generally weaker relationship between ERPF and GFR with fructosamine than with HbA_{1c} supports this conclusion.

The exact mechanism of hyperfiltration is not known. Animal studies in experimental diabetes indicate decreased afferent arteriolar tone.[22] The role of decreased distal sodium delivery, consequent upon systemic hyperinsulinism, in reducing tubuloglomerular feedback receives tentative support from work in man.[23] The factors that modulate afferent arteriolar tone are uncertain. Mogensen *et al.* found a close correlation between renal size and GFR,[5] which confirmed previous findings that have lead to a search for growth factors affected by hyperglycaemia.[24] Octreotide, a somatostatin analogue, administered to Type 1 DM patients, significantly reduced GFR, plasma flow, renal size and the serum levels of IGF-1, without affecting glycaemic control.[25] However octreotide is pleiotropic. IGF-1 when administered exogenously to healthy volunteers increases GFR and ERPF[26] and IGF-2 levels have been linked in a small study in children to hyperfiltration, hyperperfusion, and renal size.[27] The complex relationship between serum IGFs, their binding proteins and receptor population render these findings difficult to interpret. As with other workers, we have not found a significant relationship between GFR, ERPF and these growth factors or two binding proteins.[28] We confirm the contrary observation that IGF-1 is inversely related to glycaemic control.[29,30]

Cystatin C, a cell growth cycle signal, is a newer serum marker for GFR, with greater sensitivity for abnormal GFR than creatinine and greater precision for following up patients with impaired GFR.[15,31] However it did not discriminate between hyperfiltering patients and those with a normal GFR.

The role of hyperfiltration in the pathogenesis of diabetic nephropathy is contested.[2,3,32,33] Many earlier investigations were hindered by retrospective design, the lack of control for long-term glycaemic markers or by being cross-sectional examinations across a broad range of duration of disease.[34,35] Our work underscores the difficulty of examining the pathogenic contribution of hyperfiltration in isolation. If hyperfiltration does exercise a role independent of glycaemic control in the pathogenesis of diabetic nephropathy it is a weak one, and its positive predictive power insufficient to justify direct intervention.

While hyperfiltration continues to present investigative challenges, its main clinical significance remains as a correlate of poor glycaemic control. Targeting glycaemic control remains the only proven means of preventing microalbuminuria.[1,36] Ongoing follow-up studies of these patients will provide further information.

Acknowledgements

The authors wish to express their appreciation to: F. Xavier and J. Bazley for considerable technical help; M. Bending, G. Spathis, S. Mojiminyi, N. Oakley, S. Nussey, G. Robb, K. Spencer, C. Macintosh and the nursing and administrative staff at each site involved. The work was supported by grants from the St Helier NHS Trust Research and Development Fund.

References

1. DCCT Study Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int* 1995; **47**: 1703–1720.
2. Rudberg S, Persson B, Dahlquist G. Increased glomerular

filtration rate as a predictor of diabetic nephropathy – an 8 year prospective study. *Kidney Int* 1992; **41**: 822.
3. Yip JW, Jones SL, Wiseman M, Hill C, Viberti GC. Glomerular hyperfiltration in the prediction of nephropathy in IDDM. *Diabetes* 1996; **45**: 1729–1733.
4. Wiseman MJ, Viberti GC, Keen H. Threshold effect of plasma glucose in the glomerular hyperfiltration of diabetes. *Nephron* 1984; **38**: 257–260.
5. Mogensen CE, Christensen CK, Pedersen MM, *et al.* Renal and glycaemic determinants of glomerular hyperfiltration in normoalbuminuria diabetics. *J Diabetic Compl* 1990; **4**: 159–165.
6. Cole BR. Measurement of renal function without urine collection. *N Engl J Med* 1972; **287**: 1109–1114.
7. Soper CPR, Xavier FR, Barron JL. A new enzymatic method for the determination of inulin (Letter). *Ann Clin Biochem* 1996; **3**: 265.
8. Soper CPR, Bending MR, Barron JL. An automated enzymatic inulin assay, capable of full sinistrin hydrolysis. *Eur J Clin Chem Clin Biochem* 1995; **33**: 497–501.
9. Smith HW, Finkelstein L, Aliminosa L. The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. *J Clin Invest* 1945; **24**: 388–404.
10. Gerbault L. Immunoturbidometry of albumin in serum, cerebrospinal fluid, and urine with a unique calibration curve. *Clin Chem* 1987; **33**: 1260–1261.
11. Teale JD, Marks V. Inappropriately elevated plasma insulin-like growth factor(IGF) II in relation to suppressed IGF I in the diagnosis of non-islet cell tumour hypoglycaemia. *Clin Endocrinol* 1990; **33**: 87–88.
12. Holly JMP, Biddlecombe RA, Dunger RA, *et al.* Circadian variation of growth hormone-independent IGF binding protein in diabetes mellitus and its relationship to insulin. A new role for insulin? *Clin Endocrinol* 1988; **29**: 667–675.
13. Schleicher ER, Vogt BW. Standardisation of fructosamine assays. *Clin Chem* 1990; **36**: 136–139.
14. Ou C-N, Rognerud CL. Rapid analysis of hemoglobin variants by cation-exchange HPLC. *Clin Chem* 1993; **39**: 820–824.
15. Newman DJ, Thakkar H, Edwards RG, *et al.* Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. *Kidney Int* 1995; **47**: 312–318.
16. Cambier P. Application de la theorie de Rehberg a l'etude clinique des affections renale et du diabete. *Annales de Medicine* 1934; **35**: 273–299.
17. Pedersen MM, Christiansen JS, Pedersen EB, Mogensen CE. Determinants of intra-individual variation in kidney function in normoalbuminuric insulin-dependent diabetic patients: importance of atrial natriuretic peptide and glycaemic control. *Clinical Science* 1992; **83**: 445–451.
18. Jones SL, Kontessis P, Wiseman M, *et al.* Protein intake and blood glucose as modulators of GFR in hyperfiltering diabetic patients. *Kidney Int* 1992; **41**: 1620–1628.
19. Christiansen JS, Frandsen M, Parving H-H. Effect of intravenous glucose on renal function in normal man and in insulin-dependent diabetes. *Diabetologia* 1981; **21**: 368–373.
20. Christiansen CK, Christiansen JS, Schmitz A, Christiansen T, Hermansen K, Mogensen CE. Effect of continuous subcutaneous insulin infusion on kidney function and size in IDDM patients: a 2 year controlled study. *J Diabetic Compl* 1987; **1**: 91–95.
21. Wiseman MJ, Saunders AJ, Keen H, Viberti GC. Effect of blood glucose control on increased glomerular filtration rate and kidney size in insulin-dependent diabetes. *New Engl J Med* 1985; **312**: 617–621.
22. Hostetter TH, Troy JL, Brenner BM. Glomerular hemodynamics in experimental diabetes mellitus. *Kidney Int* 1981; **19**: 410–415.
23. Hannedouche TP, Delgado AG, Gnionsahe DA, Boitard C, Lacour B, Grunfeld JP. Renal hemodynamics and segmental tubular reabsorption in early type 1 diabetes. *Kidney Int* 1990; **37**: 1126–1133.
24. Mogensen CE. Glomerular filtration rate and renal plasma flow in normal and diabetic man during elevation of blood sugar levels. *Scand J Clin Lab Invest* 1971; **28**: 177–182.
25. Serri O, Beauregard H, Brazeau P, *et al.* Somatostatin analogue, octreotide, reduces increased glomerular filtration rate and kidney size in insulin-dependent diabetics. *J Am Med Assoc* 1991; **265**: 888.
26. Hirschberg R, Brunori G, Kopple JD, Guler H-P. Effects of insulin-like growth factor I on renal function in normal men. *Kidney Int* 1993; **43**: 387–397.
27. Johansson B-L, Berg U, Freyschuss U, Hall K, Troell S. Factors relating to renal haemodynamics in young type-1 diabetes mellitus patients. *Pediatr Nephrol* 1990; **4**: 589–592.
28. Hoogenberg K, ter Wee PM, Lieverse AG, Sluiter WJ, Dullaart RPF. Insulin-like growth factor I and altered renal hemodynamics in growth hormone deficiency, acromegaly and type 1 diabetes mellitus. *Transplant Proc* 1994; **26**: 505–507.
29. Merimee TJ, Gardner DF, Zapf J, Froesch ER. Effect of glycaemic control on serum insulin-like growth factors in diabetes mellitus. *Diabetes* 1984; **33**: 790–793.
30. Amiel SA, Sherwin RS, Hintz RL, Gertner JM, Press CM, Tamborlane WV. Effect of diabetes and its control on insulin-like growth factors in the young subject with type 1 diabetes. *Diabetes* 1984; **33**: 1175–1179.
31. Kyhse-Andersen J, Schmidt C, Nordin G, *et al.* Serum cystatin C, determined by a rapid, automated particle-enhanced turbidometric method, is a better marker than serum creatinine for glomerular filtration rate. *Clin Chem* 1994; **40**: 1921–1926.
32. Chiarelli F, Verrotti A, Morgese G. Glomerular hyperfiltration increases the risk of developing microalbuminuria in diabetic children. *Paediatr Nephrol* 1995; **9**: 145–148.
33. Poirier JY, Moisan A, Le Cloirec D, Maugendre P, Allanic H. Renal haemodynamic factors in incipient uropathy in IDDM patients without nephropathy: A 7 yr prospective study. *Diabetologia* 1996: A42.
34. Lervang H-H, Jensen S, Brochner-Mortensen J, Ditzel J. Early glomerular hyperfiltration and the development of late nephropathy in Type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1988; **31**: 723–729.
35. Mogensen CE. Early glomerular hyperfiltration in insulin-dependent diabetics and late nephropathy. *Scand J Clin Lab Invest* 1986; **46**: 201–206.
36. Euclid Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet* 1997; **349**: 1787–1792.

